

Nephronophthisis: *INVS* Gene Sequencing

Test Code: SINVS

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

Nephronophthisis, an autosomal recessive cystic kidney disease, is the most frequent monogenic cause of renal failure in childhood. There are four forms of nephronophthisis caused by mutations in four different genes. Clinically, there is a statistically different age at onset at end-stage renal disease: terminal renal failure develops at median ages of 13 years, 1 year, 19 years, and 11-34 years in NPHP1, NPHP2, NPHP3, and NPHP4 respectively. Hallmarks of familial nephronophthisis are tubular basement membrane disruption, interstitial lymphohistiocytic cell infiltration, and development of cysts at the corticomedullary border of the kidneys. The histology in later stages of NPHP always merges into a chronic sclerosing tubulointerstitial nephropathy, which is found in chronic renal failure of all origins.

Nephronophthisis 2

In one study, individuals with infantile nephronophthisis (NPHP2) presented within the first months of life with severe renal failure and acidosis, which could be associated with hypertension and/or polyuria and/or severe cholestatic liver disease. A renal biopsy, performed in all patients, showed similar features characterized by a diffuse chronic tubulointerstitial nephritis and particularly by the presence of microcystic dilatation of proximal tubules and Bowman space. Progression of the renal disease was extremely rapid and patients can reach end-stage renal failure before the age of 2 years (11 to 22 months).

In another study, phenotypic presentation ranged from a Potter-like syndrome to hyperechogenic kidneys, renal insufficiency, hypertension, and hyperkalemia. Affected individuals showed rapid deterioration of kidney function, leading to end-stage renal failure within 3 years. The manifestations range from prenatal fetal oliguria and oligohydramnios resulting in postnatal respiratory failure and death to postnatal onset of disease later than 30 months of age. None of the postnatally diagnosed patients had a history of either oligohydramnios or neonatal respiratory symptoms. All affected individuals developed anemia, hyperkalemic metabolic acidosis, and increased serum creatine. None of the affected subjects had polyuria, polydipsia, or associated ocular or hepatic complications.

The specific clinical features of this disease are its early onset and rapid progression to end-stage renal failure. Pathologically, it differs from later-onset nephronophthisis by the absence of medullary cysts and thickened tubular basement membranes and by the presence of cortical microcysts. NPHP2 is caused by mutations in the *INVS* gene (also known as *NPHP2*) (9q31). The protein product of the *INVS* gene, inversion, has been shown to interact with that of the *NPHP1* gene, nephrocystin.

For patients with suspected infantile nephronophthisis, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

[Click here](#) for the OMIM summary on this condition.

Genes

[INVS](#)

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of infantile nephronophthisis
- Carrier testing in adults with a family history of infantile nephronophthisis

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood (EDTA)**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml)

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: Saliva**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Deletion/duplication analysis of the *INVS* genes by CGH array is available for those individuals in whom sequence analysis is negative.
- [Custom diagnostic mutation analysis](#) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.